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The Role of Oxidative Stress in Metals Toxicity/ Mitochondrial Dysfunction as a Key Player

Hassan Ghasemi[1], Farshad Rostampour[1], Akram Ranjbar[2]✉

[1]Student Research Committee, Hamadan University of Medical Sciences, Hamadan, Iran.
[2]Department of Toxicology and Pharmacology, School of Pharmacy, Hamadan University of Medical Sciences, Hamadan, Iran.

Abstract

Metals can cause oxidative stress by increasing the formation of reactive oxygen species (ROS), which make antioxidants incapable of defiance against growing amounts of free radicals. Metal toxicity is related to their oxidative state and reactivity with other compounds. However, several reports about metals have been published in the recent years. Mitochondria, as a site of cellular oxygen consumption and energy production, can be a target for metals toxicity. Dysfunction of Mitochondrial oxidative phosphorylation led to the production of some metals toxicities metals through alteration in the activities of I, II, III, IV and V complexes and disruption of mitochondrial membrane. Reductions of adenosine triphosphate (ATP) synthesis or induction of its hydrolysis can impair the cellular energy production. In the present review study, the researchers have criticized reviews and some evidence about the oxidative stress as a mechanism of toxicity of metals. The metals disrupt cellular and antioxidant defense, reactive oxygen species (ROS) generation, and promote oxidative damage. The oxidative injuries induced by metals can be restored by use of antioxidants such as chelators, vitamin E and C, herbal medicine, and through increasing the antioxidants level. However, to elucidate many aspect of mechanism toxicity of metals, further studies are yet to be carried out. **[GMJ. 2014;3(1):2-13]**

Keywords: Metals; Mitochondrial Dysfunction; Oxidative Stress; Reactive Oxygen Species

Introduction

Reactive oxygen species (ROS) are the most important group of radical species [1,2]. ROS and reactive nitrogen species (RNS) are known to play a dual role in biological organisms, since they can be either harmful or beneficial to living systems [3]. One further beneficial example of ROS at low concentrations is the induction mitogenic response. In contrast, at high concentrations, ROS can be important mediators of damage to cell structures, including lipids in cell membranes, proteins and nucleic acids [4]. Antioxidant actions of non-enzymatic antioxidants and antioxidant enzymes correct the adverse effects of ROS [5]. Oxidative stress can be defined most simply as the imbalance between the production of ROS, RNS capable of causing peroxidation of lipid layer of cells and the body's antioxidant defense [6].

There is some evidence showing metals such as iron, copper, cadmium, chromium, lead, mercury, nickel, vanadium and aluminum can produce ROS and RNS through lipid peroxidation, DNA damage, depletion of sulfhy-

GMJ

Fax: +98 731 2227091
PO Box 7461686688
Email:info@gmj.ir

✉ **Correspondence to:**
Akram Ranjbar, School of Pharmacy, Hamadan University of Medical Sciences, Hamadan, Iran
Telephone Number: (+98) 811-8380031
Email Address : a.ranjbar@umsha.ac.ir

dryls, and altered calcium homeostasis [7,8]. In metabolism of oxygen in aerobic organisms, the mitochondrial respiratory chain is the major source of intracellular ROS generation and at the same time, an important target for the damaging effects of ROS and RNS [9,10].

The interaction of diverse macromolecules with ROS/RNS may impair the function of these organelles and may directly influence cell viability and trigger cell death [10,11]. The decline of mitochondrial respiratory function may also be caused by damages to the effect of direct free radicals on proteins, lipids and other macromolecules, as well as the effects of the mutant oxidatively damaged in mtDNA [11,12]. The mitochondrial transcription could be sensitive to free radical attack, to lipid peroxidation products, or to both. It has been proposed that mitochondrial impairment being the result of oxidative-induced damage plays a critical role in the metals toxicity [13,14]. The overall objective of this paper is to provide a concise and current review of the effects of metals toxicity on mitochondrial function and oxidative stress.

Metals-induced oxidative stress

Free radicals are defined as atoms or molecules that contain one or more unpaired electrons; the toxicity of many xenobiotic, especially metals are associated with the production of free radicals, which are in turn toxicant and implicated in the pathophysiology of many diseases [6].

The possible role of oxidative damage in pathology of metals may contribute to their toxicity [15]. Increased rates at ROS generation have often been suggested to contribute to the toxicity of high levels of several other metals, including lead, cobalt, mercury, nickel, cadmium, molybdenum, vanadium, chromium and aluminum, as well as other elements such as selenium and arsenic [16]. However, the evidence for a primary role of oxidative stress in toxicity for the elements in question is not particularly convincing. For example, although increased lipid peroxidation has often been demonstrated in isolated cells exposed to metals, or in tissues from animals poisoned by metals, this peroxidation may be a consequence of tissue injury and GSH depletion cause by the metals rather than on early contributor to the metal toxicity [17,18]. Several studies have focused on metal-induced toxicity and carcinogenicity, emphasizing their role on the generation of ROS / RNS in biological systems [18].

Mitochondria: The major source cellular oxidative stress

As estimated [19], some 0.2–2% of the oxygen taken up by cells is converted by mitochondria to ROS, mainly through the production of superoxide anion. Mitochondria consume 85–90% of a cell's oxygen to support oxidative phosphorylation, the major-energy production system in cells that works through oxidation of fuels through the synthesis adenosine triphosphate (ATP) [20].

Hence, the mitochondrial respiratory chain serves as a major source of ROS, derived from the disproportionation of superoxide anions [21]. Within mitochondria, it is the electron transport chain that is the main source of ROS [22]. The sites of ROS production along the chain have been subjected to many studies [23-25]. Recent findings show that two major sites of superoxide production are at complex I and complex III [26,27]. As described in previous studies [6,28,29], the term oxidative stress refers to both oxidative damage and oxidative stress impact on signaling, transcriptional control and other normal processes within cells; the term has also encompassed the effects of oxidants such as RNS.

In mammalian tissues, there are at least three distinct superoxide dismutase (SOD) isoenzymes, including one manganese form (Mn-SOD) present in the mitochondrial matrix and two copper and zinc forms (Cu,Zn-SOD), one of which is located only in the cytosol and the other one is in various extracellular fluids, respectively [30]. SOD plays a key role in catalyzing the dismutation of $O2^{\bullet-}$ to O2 and H2O2. Glutathione peroxidase (GPx) and catalase (CAT), remove hydrogen peroxide. In the presence of transition metals, H2O2 can be reduced to the extremely reactive OH [31,32]. Metabolizing water and corresponding alcohols (ROH) need to reduce H2O2 and a wide range of organic hydroperoxides (ROOH) by

some catalyzing reactions through GPx. Another abundant reactive radical is Nitric oxide (NO°). NO° acts as an important oxidative biological signaling molecule, having an important role on a large variety of diverse physiological processes. These include neurotransmission, blood pressure regulation, defense mechanisms, smooth muscle relaxation and immune regulation [33,34]. NO° is enzymatically generated by the actions of nitric oxide synthases (NOS) and has a half-life of only a few seconds in an aqueous environment. Under these conditions, Peroxynitrite anion ONOO° is an oxidizing free radical produced by NO° and the superoxide anion, being able to cause DNA fragmentation and lipid peroxidation [34,35].

Metal induced mitochondrial dysfunction and oxidative stress

Chromium

Chromium (Cr) is a chemical widely used in steel, alloy, cast, irons, chrome, paints, metal finishes and wood treatment. Cr is one of the important causes of allergic dermatitis and has toxic and carcinogenic effects on humans and animals [36-38]. Chromate plating and other hexavalent Cr (VI) exposure can occur in several industrial uses such as chromate pigments, chromate-based corrosion inhibitors, stainless steel machining and welding, etc [37,39]. The authors have reviewed recent in vitro and in vivo effects of oxygen scavengers, glutathione vitamin B2, vitamin E and vitamin C on chromate-induced injuries including DNA damage, lipid peroxidation, enzyme inhibition, cytotoxicity and mutagenesis. Also, Chromium overdoes occurs in the workplace primarily in the valence forms Cr (VI) and Cr (III) [40]. Inhalation of hexavalent chromium can result in several disorders such as pulmonary fibrosis, chronic bronchitis, lung cancer, occupational asthma and others [41-45]. Cr (VI) can also generate highly reactive oxidant such as peroxynitrite. In fact, Cr(VI) reduction results in several oxidants: (a) Cr(V) can directly oxidize cell components, (b) Cr(IV) catalyzes robust hydroxyl radical (HO°) generation in Fenton-like reactions with H2O2; and, (c) some enzymes simultaneously reduce Cr(VI)to Cr(V) and generate superoxide (O2°−) [46-48]. In previous studies, the results showed that Cr (VI) exposure significantly inhibits the activity of core mitochondrial functions (aconitase, complexes I and II) in both cultured cells and bronchial epithelium [49]. The inhibition of mitochondrial core protein results in inhibits of electron transfer chain and thereby impaired oxygen reduction. These phenomena lead to radicals' formation and oxidative stress [50]. The results of a study showed that total blood Cr level, SOD level, lipid peroxidation level and DNA damage were significantly higher and GSH level was significantly lower in exposed group as compared to the unexposed group [50]. Also, the studies showed that the toxicity of Cr (III) is mainly associated with cross linking mechanism which leads to multiform DNA damages, e.g., strand breakage, DNA–protein cross-links, DNA–DNA cross-links, Cr–DNA adducts and base modifications in cells [51-54]. Only chromium (VI) does not react with DNA in vitro, or in isolated nuclei. However, once inside the cell, in the presence of cellular reductants, it causes a wide variety of DNA lesions including Cr-DNA adducts, DNA-protein crosses links, DNA-DNA cross links and oxidative damage. Within the cell, glutathione rapidly forms a complex with Cr (VI), followed by a slow reduction of Cr (VI) to yield Cr (V). In addition, superoxide can further reduce Cr (VI) to Cr (V), which can further catalyze the demonstration of H2O2. Thus, it leads to the creation of DNA damaging hydroxyl radical [55,56]. Also, Cr is a ROS promoting agent, resulting in mitochondrial damage that leads to apoptosis and carcinogenicity. For example, in vivo, Cr (VI) exposure results in apoptosis, mitochondrial instability, release of cytochrome c and at least initiation cell disruption [57-59].

All in all, effective Cr chelating or elevated cellular antioxidation is the most useful way of treating Cr-induced oxidative injury, leading to the prevention of neurodegenerative disorders and chronic diseases [57,58].

Cadmium

Cadmium (Cd) is a highly toxic metal of occupational and environmental concern due to

its widespread contamination of sites worldwide and long biological half-life (10 to 30 years) [59]. In Japan, Itai-Itai disease (sever Cd poisoning) was observed when Cd was discharged from a mine into a river used to supply drinking water. The organism is widely distributed in the environment and elevated exposure can be of both natural and anthropogenic origin [60,61]. Exposure occurs mainly via food, in particular plant-derived food and certain seafood, and from tobacco smoke [62]. Several studies showed that low-level environmental exposure to Cd has adverse health effect on kidney and bone; In addition, recent studies have reported higher risk of cancer and increased mortality [63]. In adults, only a few percentage of the ingested Cd is absorbed in the gastrointestinal tract. In contrast, Young adults have a higher absorption, apparently coupled with a different mechanism of uptake [64]. Cd-increased ROS lead to lipid peroxidation and DNA damage ROS has been implicated in chronic Cd nephrotoxicity [65-67], immunotoxicity [68] and carcinogenesis [69]. Some indirect mechanisms involve in radical production by Cd. Several mechanisms have emphasized the role of Cd in generation of free radicals. Disruption of the cellular antioxidant system by glutathione depletion is one of them [70,71]. Induction of inflammation in the liver is another important mechanism that proposed for Cd-induced oxidative stress [65]. Cd-induced inflammatory mediators such as IL-1β, TNF-α, IL-6, and IL-8 are generated by the activation of the resident macrophages of the liver (Kupffer cells) [72]. It has been suggested that Cd produce ROS by binding to protein thiols in the mitochondrial membrane and affect mitochondrial permeability transition and inhibit respiratory chain reaction [73,74]. Cd inhibit mitochondrial complex III, resulting in accumulation of semiubiquinones at the Coenzyme Q sites, which lead to one electron to molecular oxygen to form superoxide anion [75]. Indeed, Cd effects on mitochondrial electron transfer are the major origin for Cd generated ROS, not only in mammalian cells, but also in plants [76]. In cells, some of transcription factors such as AP-1 and NF-κB are sensitive to oxidative stress. The activation of these transcription factors by Cd has been shown in intact animals and cultured cells [77-79]. In addition, the activation of MAPKs by Cd is associated with ROS production in intact animals (80) in cultured cells [81,82], which in turn plays an important role in Cd-induced apoptosis to eliminate oxidative damaged cells [83]. It is hypothesized that during acute and chronic Cd exposure, adaptation mechanisms are induced to offset Cd-induced ROS, oxidative damage and mitochondrial dysfunction [70,71].

Adaptation to chronic Cd exposure reduces ROS production, but acquired Cd tolerance with aberrant gene expression plays important roles in acute, chronic Cd toxicity and apoptosis [77,84]. In addition, Cd modulates protein kinase, transcription factors, MAPK, mitochondria, caspases, and ROS pathways all seem to have a role in Cd-induced apoptosis and cancer [78,80]. Cooperatively, efficient chelation of the element and/or supplementing antioxidative materials is the preferred medical treatment for reducing various toxic and effects followed by Cd exposure [65,70].

Lead

Lead (Pb) is a common agent that causes environmental and industrial pollutant. Pb is one of the most commonly used metals in industry and its toxicity is of concern to public health due to the persistence of lead in the environment. Pb has been found to produce several toxic biochemicals [85].

Liver, kidney and brain are the major organ that affected by Pb [86]. Long term exposure to this bio-toxicant leads to its accumulation in these organs with maximum concentration in different tissues [87]. The neurotoxic effect of Pb, particularly in the developing brain is a matter of serious concern and behavioral abnormalities, learning impairment, decreased hearing and impaired cognitive functions in humans and experimental animals have been recorded with blood Pb levels as low as 10 g/dl [88]. Several mechanisms have been proposed to explain the Pb induced toxicity, but no mechanisms have been yet defined explicitly [85]. Results from recent studies showed that oxidative stress is one of the important mechanisms of toxic effects of Pb [85]. Also,

Pb exposure led to various degrees of increased lipid peroxidation with tissue specific changes in liver [89,90], kidneys [89,91] and brain [89,92,93]. Treatment of Pb -exposed rats with tocopherol and ascorbic acid did not reduce tissue Pb burden, but lowered the lipid peroxidation levels, revealing their antioxidant potential in lead related oxidative stress. In addition Pb is shown to induce changes in the composition of red blood cell (RBC) membrane proteins and lipids, and inhibit hemoglobin synthesis [94,95]. Several antioxidant enzymes and molecules such as reduced glutathione (GSH) concentration, GPx, SOD and CAT activities, have been used to evaluate Pb -induced oxidative damage in animal and human studies [89,95,96]. Pb, because of its affinity to SH group, is known to inhibit ALAD (the second enzyme in the heme biosynthesis pathway and catalyzes condensation of two molecules of aminolevulinic acid (ALA) to a porphobilinogen.), resulting in accumulation of ALA. ALAD has been suggested as a sensitive index of the effect of Pb exposure on hematological system [97,98]. Hematological system is one of the important targets for Pb induced toxicity. The effects of Pb on this system result in decreased heme synthesis and anemia [99]. High concentrations of oxygen, autoxidizability of hemoglobin, vulnerable membrane components to lipid peroxidation and limited capacity to repair their damaged components, are factors that make RBCs sensitive to oxidative damage [100]. Previous studies of correlation between clinical indicators of Pb poisoning and oxidative stress parameters in controls and Pb-exposed workers showed that there was a disruption of prooxidant/antioxidant balance in Pb-exposed workers [101,102]. However, several studies suggested ALA as a possible source [103]. Inhibition of ALAD by lead results in accumulation of ALA during heme biosynthesis. In next step, accumulated ALA has been shown to undergo metal-catalyzed auto-oxidation giving rise to the formation of superoxide ($O_2^{\bullet -}$), H_2O_2 and ALA [103]. All in all, there may be two independent sources of Pb-induced oxidative damage; the first is the pro-oxidative effect of δ-ALA, and the second is connected with the direct effect of Pb on membrane lipids and mitochondrial dysfunction [104-106]. Pb depolarizes cell mitochondria due to the opening of permeability transition pore, resulting in cytochrome c release, caspase activation, and apoptosis. In Pb induced apoptosis, the opening of mitochondrial permeability transition pore is due to oxidative stress [107,108].

There are many studies suggesting possible clinical applications of exogenous antioxidants in the treatment of toxicity induced by Pb exposure. For example, treatment with ascorbic acid or a-tocopherol and N-acetylcystein was found to reduce the level of ROS-initiated damage and their combined administration restored normal mitochondrial function in Pb -supplemented rats [89,109,110].

Aluminum

Aluminum (Al) is the third most abundant element and distributed widely in the biosphere. Al constitutes approximately 8% of the earth crust exceeded only by oxygen 47% and silicon 28% [8]. Several mechanisms have been proposed to explain the toxicity of Al, none supported by convincing data from in vivo experiments [111]. Al^{3+} ions cannot stimulate lipid peroxidation or other free radical reactions which is not surprising because of their fixed valence [112]. However, if peroxidation in liposomes erythrocytes, synaptosome somylein, or microsomes is stimulated by adding fe^{2+} ions, the simultaneous addition of Al^{3+} increases the per oxidation rate. It may be that Al^{3+} ions bind to membranes and cause a subtle rearrangement of membrane lipids that aids the propagation of lipid per oxidation, this action of Al^{3+} might contribute to its neurotoxin properties, since the brain is sensitive to oxidative damage [113,114]. Injection of large dose of aluminum salts into animals has been claimed to increase brain lipid peroxidation levels. And injection of aluminum-containing vaccines into mice caused a transient rise in brain aluminum levels [114,115].

Also, Aluminum accumulation is thought to be related to renal impairment, anemia and other clinical complications in hemodialysis patients and they showed that patients undergoing hemodialysis present platelet dysfunc-

tion and lipid peroxidation [116,117].
However, increased ROS were reported during Al exposure, which was attributed to electron leakage, enhanced mitochondrial activity and increased electron chain activity. Mitochondria contribute too much of core human metabolism, including oxidative phosphorylation, the tricarboxylic acid (TCA) cycle, fatty acid oxidation, iron sulfur center and heme biosynthesis, and amino acid metabolism [118]. These are in addition to the well-established role of the mitochondria in energy metabolism and regulation of cell death [119]. Also, previous studies revealed that Al induced imbalance in this steady state allows the induction and effects of mitochondrial dysfunction [120,121]. Since Al induces oxidative damage resulting in an increase of ROS production, it is possible that Al-induced ROS are involved in mitochondrial instability, and release of cytochrome c [122,123]. Although the administration of antioxidant materials is widely used in Al intoxication. vitamin C, E and efficient chelating of the element supplementing is useful, that Al induced, neurode generative disorders such as Alzheimer diseases [124-127].

Conclusion

One cannot avoid the generation of ROS, because it is a result from aerobic life. ROS is produced in mitochondrial function [128]. ROS are known not only to attack DNA, but additional cellular components such as proteins and lipids, leaving after reactive species that can, in turn, bind to DNA bases [129,130]. This implicates such damage in the etiology of many diseases such as cancer [131,132]. Toxic metals (lead, Cd, Cr, Al, mercury and arsenic) are widely found in our environment [17].
Humans are exposed to these metals from numerous sources, including contaminated air, water, soil and food [16]. There are some new studies, showing that transition metals act as catalysts in the oxidative reactions of biological macromolecules. So, metals act their toxicities roles through mitochondrial dysfunction and oxidative tissue damage [16,18,133,134]. Although, ROS has been implicated in activation of an extrinsic cascade, the correlation of ROS, caspase activation and p38 in metals-induced apoptosis, requires further investigation. A potential role for ROS, the mitochondria, and activation of several signaling pathways (MAPK and p53) have been established for several metals [135,136]. To clarify how ROS induce cellular response and signal transduction is quite important for understanding of the mechanisms of metal-induced carcinogenesis. Certainly, many researchers have implicated the involvement of ROS signaling in metal-induced carcinogenesis and cell death over the last decade. However, they did not provide a direct evidence of the correlation between ROS and metal-induced apoptosis and carcinogenesis [137-139].
Data suggest that antioxidants may play a important role in abating some hazards of metals [8,140]. Currently, treatments against metals toxicity include the use of chelating agents, metallothionein, and antioxidant therapy with melatonin, vitamin E, vitamin C, N-acetylcysteine and herbal medicine [7,141-144]. The effectiveness of an antioxidant based treatment approach is dependent on understanding the mechanisms by which metals cause mitochondrial dysfunction and other health conditions.
Although metal-induced oxidative stress does not explain all of the cell disruptions' caused by metals, accumulating evidence emphasizes the protective effect of antioxidants in the setting of metal-induced toxicity. The effectiveness of an antioxidant-based treatment approach is dependent on understanding the mechanisms by which metals cause cancer and other health conditions. In this regard, future studies should focus on defining cellular and molecular mechanisms of metal-induced oxidative injuries, developing efficient biomarkers, and identifying individuals with increased susceptibility to metal exposure.

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